REMARKS

Reconsideration of the above-identified application is respectfully requested. Claims 1-9 directed to a human intervertebral disc cell culture have been cancelled.

Claims 10-11, 13-15, and 18 directed to a therapeutic composition for use in treating human disc diseases have been amended.

Claims 19-34 to a method for treating an intervertebral disc disease in a human patient remain for prosecution.

As noted above, the remaining claims are directed to therapeutic compositions of the cultured human intervertebral disc cells for use in treating human intervertebral disc diseases and methods of treating human intervertebral disc diseases by implanting the cultured human intervertebral disc cells into a target disc area needing treatment.

Claim Rejection - 35 U.S.C. § 112,¶1

Claims 10-34 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner has raised the following issues:

1. The specification does not disclose if the cultures cells are annulus or nucleus cells, if the implanted cells were dedifferentiated cells or if the cells were cultured such that re-expression of extracellular matrix proteins were obtained prior to implantation.

2. Whether the implanted cells were actually dividing, or whether the cells recapitulated the *in vivo* biosynthetic the extra cellular matrix proteins profiles.

3. In view of the teachings of Aigner *et al.* and Guilak *et al.*, would it have required undue experimentation for one of skill in the art to provide an expanded

population of the appropriate intervertebral disc cell type and use the expanded population in a method for treating disc disease by implanting the cells into intervertebral disc tissue.

Response to §112, ¶1 Issues

Issue 1. The Examiner states that the specification does not disclose if the cultured cells are annulus or nucleus cells, if the implanted cells or differentiated cells or if the cells were cultured such that re-expression of extra cellular matrix proteins was obtained prior to implantation. Thus, it is not known which cells were used or what the phenotypic profile of the cells were at the time of implantation.

Implant cells were derived from the annulus of an adjacent sand rat disc. Technically the cells which were cultured from the sand rat disc for later implantation became de-differentiated based on the fact that they assumed a spindle-shape in monolayer culture.

It is important to remember that in man, and in several other species, the true cells which derive from the notochord during development and which form the nucleus do not persist throughout life. In humans, these cells, which have a very unique morphology and cell shape, disappear in infancy and are replaced by chondrocyte-like cells. This has been documented by the earlier studies by Walmsley, *The development and growth of the intervertebral disc,* Edinburgh Medical J., 60:341-364, 1953); Taylor and Twomey, *"The development of the human intervertebral disc."* Chap. 2 in Vol.1, pp 39-82, The biology of the Intervertebral Disc. P.Ghosh, ed. CRC Press, Boca Raton, FL, 1988*);* and Butler, *"Comparative anatomy and development of the mammalian disc,"* P. Ghosh, ed. CRC Press, Boca Raton, FL. 1988.

As recently discussed by Errington, *et al*, J Anat. 192:369-378, 1998, characterization of cytoplasm-filled processes in cells of the intervertebral disc), it is not known whether these chondrocyte-like cells are derived form dedifferentiation of the notochordal cells, or whether the notochordal cells die and mesenchymal cells invade the nucleolus. In any event, the central region of the disc is termed "nucleus" and does have a characteristically different type of

extracellular matrix. Cells within this region, hover, are probably descendents of the annulus, and in the human are not "nucleus" cells. Copies of the papers are attached.

Although the term "nucleus" is often used in the medical literature, it more accurately describes the features of the matrix which remains in the central area of the disc, and not the cells which are present within this matrix in the human after infancy.

Issue 2. The Examiner states that it is not apparent from statements on page 17 of the specification whether the implanted cells were actually dividing or whether the cells recapitulated the in vivo biosynthetic the extra matrix protein profiles. Thus, from the disclosed experiments, it is not known which cells were expanded in vitro and whether the implanted cells divided and expressed extra cellular matrix proteins which were representative of those observed in a normal intervertebral disc in vivo.

With respect to the matrix made by the reimplanted cells, there are no commercial antibodies with which the matrix can be assessed which surrounds the labeled engrafted cells. It should be noted, however, that the matrix laid down by the cells native to that disc, so this provides evidence that they were making an appropriate type of extracellular matrix. Histologic examination of routinely stained sections provides the best method to date of examining cells implanted in the sand rat disc.

All cells which were dividing in tissue culture during exposure to BrdU become labeled with BrdU which it is incorporated into their DNA. All daughter cells which result from subsequent divisions of these cells are also labeled. Thus, one cannot distinguish between an engrafted labeled cell and the progeny of one of these engrafted labeled cells. Since considerable extracellular matrix surrounds the cells, it is likely (although we cannot prove it) that at least some of these cells resulted from subsequent cell divisions.

Issue 3. According to the Examiner, in view of the teachings of Aigner *et al.* and Guilak *et al.*, would it have required undue experimentation for one of skill in the art to provide an expanded population of the appropriate intervertebral disc cell type and use the expanded

population in a method for treating disc disease by implanting the cells into intervertebral disc tissue.

With respect to the citation of the paper by Aignor *et al.*, it should be noted that this paper was intended to look at cells within the endplate. The endplate is made of cartilage and is not composed of disc tissue. Note that the authors were careful to include fetal (in which there is a real notochordal nucleus cell population). The cells which are shown in the "nucleus" illustration in Figure 2N are chondrocyte-like in shape are definitely not notochordal nucleus cells.

With respect to the issues of the complex biology and biomechanical nature of the disc, there are no known animal study or human study in which all of these issues have been definitely quantified. It is expected that autologous cell implantation will help identify cell populations implanted in certain areas of the disc and thus expand our understanding of these cells.

With respect to the comments on the bottom of page 5 regarding extrapolation of findings from animal models to human, the examiner is corrected that direct extrapolation is not possible in any study. Note however, that the two cited papers (one of which is from the applicants' laboratory - Frick *et al.* are studies of disc transplantation, and do not deal at all with cell disc culture or autologous disc cell implantation. Thus, they are not directly relevant to this patent application. Disc transplantation does not work as shown in the publication by Frick; hence, the cell-based approach described in the patent application was developed.

However, the scientific record is built upon animal trials being an important component of any pharmaceutical or surgical methodology that is developed for the purpose of being taken directly into the medical armamentarium. Clinical trials would be the next step to answer many of the questions the examiner has raised in the office action. The studies with cell implantation in the sand rat show that this is a feasible endeavor which merits consideration as a therapeutic modality. This is especially true in light of recent rabbit implantation studies by Nishiida *et al.*, copy attached.

In summary, while applicants do not argue that no experimentation to practice the invention is required the issues raised by the examiner are clarified by the discussions above

which illustrate that there is sufficient guidance in the specification such that undue experimentation for one skilled in the art is not required. It is therefore respectfully submitted that the methods of treating disc disease meet the requirements of 35 U.S.C. §112, ¶1.

Claim Rejection - 35 U.S.C. § 112,¶2

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Since claims 1-9 have been cancelled, this rejection is now moot.

Claim Rejections - 35 U.S.C. § 102

Claims 1-9 and 10-11 and 13-15, 17, and 18 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Gruber et al. (Exp. Cell Res. 235:13-21, 1997).

Regarding Claims 10-11 and 13-15, 17 and 18, the applicants' have amend independent claims 10 and 14 to include the limitations of claims 12 and 16 respectively. Accordingly, the rejection of claims 10-16 and 18 have been overcome. Regarding Claims 1-9, these claims have been cancelled; thus, the rejection of claims 1-9 is moot.

Claims 1-9 and 10-11 and 13-15, 17, and 18 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Gruber et al. (Matrix Biology, 16:285-288, 1997).

Regarding Claims 10-11 and 13-15, 17 and 18, the applicants' have amend independent claims 10 and 14 to include the limitations of claims 12 and 16 respectively. Accordingly, the rejection of claims 10-16 and 18 have been overcome. Regarding Claims 1-9, these claims have been cancelled; thus, the rejection of claims 1-9 is moot.

Claims 1-9 and 10-11 and 13-15, 17, and 18 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Chelberg et al (J. Anat. 186:43-53, 1995)..

Regarding Claims 10-11 and 13-15, 17 and 18, the applicants' have amend independent claims 10 and 14 to include the limitations of claims 12 and 16 respectively. Accordingly, the rejection of claims 10-16 and 18 have been overcome. Regarding Claims 1-9, these claims have been cancelled; thus, the rejection of claims 1-9 is moot.

Double Patenting

Claims 1-18 (now claims 10-11, 13-15, and 18) stand rejected over the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-11 of U.S. Patent No. 6, 080,579.

An appropriate terminal disclaimer is enclosed herewith. It is therefore respectfully submitted that the timely filing of this terminal disclaimer overcomes this rejection.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner For Patents, Washington, DC 20231, on February 13, 2001.

Janet F. Moore